Fresh-frozen vs. irradiated allograft bone in orthopaedic reconstructive surgery

Costain DJ, MSc FRCS(C)[*], Crawford RW, DPhil, FRACS (Orth)[*†]

[*] Institute of Health and Biomedical Innovation
Queensland University of Technology
Brisbane, Queensland
Australia

[†] Orthopaedic Research Unit
The Prince Charles Hospital
Chermside, Queensland
Australia

Proofreading/Reprint requests:
Professor Ross Crawford
5th Floor, Clinical Sciences Building
The Prince Charles Hospital
Rode Road
Chermside, Queensland
Australia 4032

(W): +61 (0)7 3139-4481
(Fax): +61(0)7 3139 4043
E-mail: r.crawford@qut.edu.au

Abstract:

The use of allograft bone is increasingly common in orthopaedic reconstruction procedures. The optimal method of preparation of allograft bone is subject of great debate. Proponents of fresh-frozen graft cite improved biological and biomechanical characteristics relative to irradiated material, whereas fear of bacterial or viral transmission warrants some to favour irradiated graft. Careful review of the literature is necessary to appreciate the influence of processing techniques on bone quality. Whereas limited clinical trials are available to govern the selection of appropriate bone graft, this review presents the argument favouring the use of fresh-frozen bone allograft as compared to irradiated bone.

Key Words:

Allograft, irradiation, fresh-frozen, impaction graft, tissue processing

Short running title:

Fresh vs. irradiated bone graft

Introduction:

Deficiencies in bone stock plague orthopaedic surgeons dealing with hip and knee revision arthroplasty, trauma, and tumour reconstruction. Bone grafting procedures serve two primary functions:

1. Provide early or immediate mechanical stability to area of bony deficiency
2. Enable reconstitution of bony deficiencies via osteoinductive, osteogenic, or osteoconductive properties.

Due to limited quantity and associated morbidity with harvesting autograft bone, as well as inferior biological and/or biomechanical characteristics of synthetic calcium substrates, allograft materials have largely been preferred in reconstructive procedures. It is estimated that over 150,000 allograft bone procedures are performed annually in the US alone.[7,56] Much controversy exists surrounding processing techniques used in allograft bone. Because of concern over immunogenicity and microbial contamination of donor tissues, terminal sterilization of the product with varying doses of γ radiation has been advocated. However, this is not without influencing both the biological as well as biomechanical integrity of the graft material. Understanding the biology of allograft bone, and the influence of variable treatment regimens on the quality of donor material is essential to optimize long-term patient outcomes with reconstructive efforts. This review will focus on the comparison between fresh-frozen and irradiated bone graft in orthopaedic surgery.

Immunogenicity:

Unlike other tissues and organs used in transplantation surgery, there is no effort to use haplotype matching with allogeneic bone. Retention of cellular debris had been suggested to play

a role in the initiation of an immunologic response leading to suboptimal graft incorporation.[60] In a dog osteochondral allograft model, frozen mismatched allografts demonstrated greater porosity (indicating revascularization), and more live cortical cells upon post-implantation retrieval analysis relative to fresh mismatched grafts.[53] This correlates with earlier reports by the same group demonstrating elevated titres of anti-HLA antibody in synovial fluid of fresh relative to frozen osteoarticular allografts in dogs.[54] Cytotoxic T lyphocytes reactive to HLA-mismatched cells have also been demonstrated in patients receiving bulk fresh-frozen allografts for tumour reconstruction surgery,[23] and these allo-reactive cells were proposed to play a role in delayed allograft incorporation.

Similar to freezing graft tissue, irradiation has also been shown to reduce the cellularity of allograft bone,[44] however, in a rat femur model, no significant difference in healing strength was demonstrated between fresh, frozen, or irradiated allograft bone at various times post transplantation.[44] In this regard, there is no scientific evidence to date to support irradiation of bone to improve graft immunotolerance and incorporation.

Sterility:

Generally, there are two common strategies used in graft retrieval to ensure product sterility:

1. Use of appropriate candidate screening, with sterile retrieval and processing, and stringent quality control testing of end product
2. Terminal sterilization, most commonly using γ irradiation in range between 10-25kGy

In the absence of terminal sterilization, strict adherence to guidelines and protocols is required, as outlined by the American Association of Tissue Banks. Despite these protocols, up to 22%

material is often discarded due to microbial contamination.[52] Infection rates using structural allograft were recently reported from a 30 year review of reconstructive tumour surgery at Harvard, revealing 121/945 infections (12.8%) in this population, in which many patients were also undergoing post-operative radiation and chemotherapy.[38] This report failed to characterize whether there was any association between the use of irradiated vs. fresh frozen allograft tissue. The use of γ irradiation has been advocated to both reduce wastage of the limited supply of allograft material, and also to increase safety of tissue transplantation in terms of infection risk to the recipient.

The estimated risk of HIV transmission with allograft bone transplantation from screened donors is 1 in 1.6 million procedures,[9] with no new reported cases since 1985.[50,57] This risk is less than the risk of transfusion with a unit of blood.[57] These cases originated from a cadaveric donor with viral titres below the limit of detection of the assay in use at the time, and as such have been used to reinforce the argument that irradiation improves safety. Similarly, 5 patients have become infected with HCV in 2002 secondary to subclinical viral titres in the donor.[11] However, the usual upper limit of γ irradiation exposure to bone allograft in the US is 25kGy, and it has been reported that up to 50kGy are required to inactivate HIV.[25,28,51] This therefore brings into question whether standard level of γ irradiation would have altered the outcome in these unfortunate cases.

Recently, there have been reports of patient morbidity, and one mortality, related to bacterial contamination of cadaveric graft material used in orthopaedic procedures.[12,13,35] A case of group A streptococcus (GAS) infection arose from a patellar tendon allograft anterior cruciate ligament

reconstruction in a young patient. Review of the tissue provider's records revealed that the non-irradiated tissue was positive for GAS prior to processing, but negative after processing. Five other recipients of tissue from the same donor failed to develop infection. In the report of 26 patients with bacterial infection secondary to orthopaedic allograft procedures, 13/26 (50%) patients were infected with *Clostridium* species, and 14 of the 26 reported cases originated from the same tissue processing laboratory.[13] Of note, irradiation of spore-forming organisms has variable efficacy in terms of bactericidal activity.[28] These reports reveal that terminal sterilization procedures on contaminated products may not be efficacious or safe, and in that respect the ability of terminal γ-irradiation to safely reduce allograft bone wastage comes into question. Further, careful review of the protocols of the tissue providers would be more appropriate rather than advocating universal γ irradiation of all products. Finally, these cases involve transplantation of tissues retrieved from cadaveric donors as compared to femoral heads obtained from live donors at primary hip arthroplasty. Up to 42% of cultures obtained from cadaveric donors are positive at the time of tissue harvesting,[14] compared to 1.2%-22% contamination of bone allograft from live donors.[52]

Biomechanical effects:

Initial stability is essential for long-term survivorship with bone grafting in weight-bearing zones, and early failure is felt to be either due to excessive compression, shear, or a combination of the two.[6,8] Several experimental reports have demonstrated the effect of γ irradiation on the biomechanical properties of allograft bone.[42] Currey and colleagues[20] showed a non-significant change in elastic modulus of irradiated human cortical bone relative to fresh-frozen graft (12-13gPa vs. 13.6-15.8gPa, respectively), moderate effect on bending strength (110-120mPa vs.

157-181mPa, respectively), and a substantial decrease in work to fracture energy (0.3-0.6 kJ/m^2 vs. 6.8-12.6 kJ/m^2, respectively) after exposure to 29.5 kGy. Although various reports have suggested minimal effect of radiation on Young's modulus of allograft bone, irradiated bone has been shown to become "embrittled", with a 64% reduction in energy to failure with 28 kGy[29]. In the same report, work to failure energy was reduced in a dose-dependent manner with escalating amounts of irradiation (6.8-23 kGy). Irradiation-induced free oxygen radicals have been shown to alter collagen backbone in human femoral allografts exposed to 36.4 kGy, reducing post-yield strength by 70-87%, and reducing fatigue strength by 87%.[1,2] Other experimentation has shown that γ irradiation causes collagen backbone scission[31] and reduces collagen cross-linking.[16] Irradiated human femoral cortical bone also showed reduced resistance to fatigue crack propagation relative to non-irradiated bone using subcritical cyclic loading stress.[39] This coincided with reduced crack-branching/microdamage distribution. More importantly, it has been suggested that the typical mode of failure of allograft material involves cyclic fatigue. Akkus and Belaney[2] tested human cortical bone irradiated with 36.4 kGy with cyclic subcritical stress to investigate fatigue stress. Elastic modulus and yield strength did not vary substantially with or without irradiation. However, energy to fracture (reduced by 86.4%), post-yield energy (reduced by 70%), and fracture strain (reduced by 60.5%) were dramatically influenced by irradiation. With low cycle fatigue testing, 254 vs. 51,938 cycles were required to failure in irradiated vs. non-irradiated tissue. In high cycle testing, 39,495 vs. >300,000 cycles in irradiated vs. non-irradiated tissue were reported. Calculated reduction in fatigue strength was 99.1% with gamma irradiation. Further, this study investigated only tensile, not compressive, shear, or tortional fatigue failure, thereby perhaps underestimating the magnitude of the weakening due to irradiation.

Less information is known about the effect of γ irradiation on cancellous bone. A report by Anderson and colleagues[3] suggested that only 60 kGy, but not lower doses of radiation (including 10, 31, and 51 kGy) weakened cancellous bone obtained from the proximal tibia of two cadaveric donors. Despite no significant alteration in failure stress or modulus, there was significant variability in their assay. The mean failure stress in non-irradiated bone averaged 6.55 (+/- 2.59) MPa, while failure stress after 31 kGy averaged less than half that of the non-irradiated control (3.00 +/- 1.84 MPa). The modulus of non-irradiated bone was 660 +/- 440 MPa, while only 270 +/- 240 MPa with 31 kGy of irradiation. Further, the cancellous bone in this study was not impacted, as is typical in the clinical scenario, leaving the results difficult to interpret. A separate study using tricortical iliac crest wedges failed to demonstrate a significant difference in compressive strength when freeze-dried non-irradiated samples were compared to irradiated samples.[61] However, fatigue, tortional, and shear strength were not analyzed in this study, and the cortical properties cannot be separated from cancellous bone with their methods.

A recent study by Cornu's group has shown that impaction grafting with fresh-frozen bone performed worse relative to freeze-dried, irradiated bone in a hip simulator model of implant stability.[18] This experimentation used subclinical loading force at 1.5x body weight for 900,000 cycles in a simulator, and no gross movement was detectable in any sample. However, micromovement was detected at 110 +/- 38μm vs. 175 +/- 26μm in fresh vs. irradiated graft, and 265 +/- 76μm vs. 81 +/- 35μm subsidence was evident in fresh vs. irradiated graft, respectively. Because small forces were placed on the graft in this experiment, it is difficult to extrapolate this to the clinical situation, where typical forces on the hip can exceed 8x body weight.[5] Further, it is

known that overimpaction of impaction graft may have deleterious effects on osteointegration,[55] and stability in this study was attributed to increased ability to impact the freeze-dried irradiated bone vs. fresh frozen.[19] Finally, an earlier study by the same group has shown 42.5% reduction in strength, 21% reduction in stiffness, and 71.8% reduction in work to failure with the same protocol for allograft irradiation.[17] Taken together, the biomechanical literature overwhelmingly demonstrates the deleterious effect of γ-irradiation on resistance to fatigue failure, suggesting caution for its use clinically.

Biological effects:

In addition to biomechanical failure, delay or lack of union at graft-host interface alters graft performance.[21] Strength is largely a product of cross-sectional area of graft. With increased absorption and porosity, there is a commensurate loss of structural strength. Incorporation of bone implies revascularization, which is integral in the process of healing. Delayed or absent vascular ingrowth results in loss of biomechanical competence and greater propensity for catastrophic mechanical failure.

Irradiation of unprocessed femoral heads produces altered marrow lipids that are cytotoxic to osteoblasts in culture.[40] The cytotoxicity observed in this study was felt to be related to 2-3 fold increases in peroxidated lipids following irradiation. Further, irradiation with 25 kGy reduces osteoblast differentiation and expression of BMP-7 when compared to non-irradiated human bone graft implanted in a nude rat model.[15] In this study, 44-58% reduction in osteoinduction was observed, with a trend towards more osteoclast cells seen in irradiated specimens. This may be related indirectly to altered collagen in irradiated samples.[24] In another animal model, no

effect was observed on incorporation of irradiated bone graft in a tibial defect model.[32] However, bone was analyzed at one time period only (12 weeks), and this model did not involve mechanical loading of the defect. Therefore, in addition to resulting in a weaker substrate, γ-irradiation of bone also appears to reduce the potential for graft incorporation, and therefore is less desirable than fresh frozen allograft bone.

Clinical studies:

Although experimental models investigate graft viability, success of union, and attachment to soft tissue bed (as summarized in Table 1), they generally do not evaluate long-term performance due to cost limitations and limited translation to human significance. In that regard, clinical evaluation of bone graft performance yields important information not obtainable in the laboratory.

The majority of the published clinical studies (summarized in Table 2) documenting results with allograft material consist of retrospective reviews of uncontrolled case-series. The healing phase following impaction allografting has been characterized from retrieval analysis of non-irradiated patients. There are three phases:

1. Neovascularization of the graft
2. Resorption of vascularized graft with osseous apposition
3. Formation of new trabeculae surrounding graft

This was demonstrated by Heeken and colleagues[33] and later by VanderDonk et al.[59] Histologic review of samples retrieved from revised femoral hip or knee components reveals areas of

persistent graft adjacent to femoral component with impaction allografting with washed, fresh frozen femoral heads. The innermost layer is present at 11 months, and areas are still visible at 48 months, indicating that mechanical integrity of graft may bear significance to long-term survivorship.[58] A similar report on femoral impaction grafting using fresh frozen graft suggests a similar phase of bone incorporation.[41] Human histology from irradiated specimens comes from Hamer's group[30] using irradiated femoral strut allografts in revision hip surgery. In biopsy specimens obtained in 5 patients ranging from 2-27 months post-operatively, initial osteoclastic resorption of non-viable bone is followed by a second wave of osteoclastic resorption with subsequent capillary ingrowth and new bone apposition. No comparison was made to non-irradiated bone.

Schureurs and colleagues[49] have shown 90% survivorship at 11.8 years with fresh frozen allograft acetabular reconstruction in 60 hips. More recently, this group had been followed to 15 years with 79% survivorship.[47] Further, 42 hips in patients <50 years old showed 80% survivorship at 20 years with the same methods.[48] Revision of deficient acetabula with Paprosky grades 3a and 3b using fresh-frozen femoral head allograft revealed 98.6% survivorship at average 6.8 years.[26] This compares with 87.8% acetabular survivorship at median 51 months using irradiated femoral head allografts with cemented cups,[10] with16/100 considered un-united by Conn criteria. Femoral impaction grafting in revision hip arthroplasty using fresh-frozen graft demonstrates 100% survivorship at 10.4 years.[46]

Robinson and team[45] reported their experience using irradiated impaction allograft bone with Exeter polished stems for revision of 57 femoral stems with loss of bone stock. They reported

only 39% radiographic evidence of graft incorporation, but no trabecular remodeling at average 27 months. Subsidence of >5mm was observed in 19.5% patients, raising concerns over the use of irradiated bone for femoral impaction grafting. This compares with a RSA study of 15 hips revised with non-irradiated allograft, which revealed 100% survivorship at 5 years, despite RSA evidence of migration in all 15 stems.[43] A recent study has reported success with the use of irradiated allograft supplemented with autologous bone marrow aspirates.[22] However, in this report, autologous bone marrow represented 40% of graft, underscoring the significant proportion of viable host-derived cells, and thereby limiting its translation to the typical setting.

Bankes and colleagues[4] reported results of revision hip arthroplasty in 38 patients (41 hips), 20 receiving fresh-frozen allograft, 18 irradiated (25-30 kGy) graft. Although not randomized, this is the closest direct comparison of clinical results using the two forms of processed graft. An average of 52 months of follow-up was available for the fresh-frozen population, with 38 months using the irradiated graft. In the former population, there were no revisions, mean of 1.72 mm stem subsidence, and 90% favorable bone changes radiographically based on criteria describe by Gie et al.[27] Comparatively, 1.93 mm subsidence and only 65% favorable radiographic changes were seen with earlier follow-up in the recipients of irradiated allograft. Six of 20 patients with fresh-frozen, and 2 of 18 with irradiated graft showed radiolucencies on x-ray. However, based on histological examination, the significance of radiolucencies does not necessarily correlate with viability of allograft bone interface.[37]

A similar study by Holt's group[34] reviewing acetabular impaction grafting, with 22 fresh-frozen grafts, 20 irradiated grafts, suggested good outcomes with either graft material. Interestingly, only 15 months follow-up were available for the irradiated graftings, compared to 30 months for

the fresh frozen graft. Furthermore, 4 patients were reported to demonstrate acetabular radiolucencies, although it was not described whether these were fresh vs. irradiated graft recipients.

Fracture is one of the most common complications with the use of bulk allografts clinically, occurring 12-20% cases. In a study comparing complications in tumour reconstruction surgery, the incidence of fracture was more than double with irradiated (39%) vs. non-irradiated (18%) bone.[36] In summary, no clinical report has ever demonstrated superiority of irradiated bone, while several reports show inferior results relative to fresh-frozen allograft bone.

The main weakness of this article is that it was not a systematic review of all available literature. Such an undertaking would be laborious given the diverse nature of this topic, as both animal and human studies, as well as in vitro and in vivo studies were reviewed. Further, the number of well-controlled studies on the topic are limited. In particular, to date there has been no head-to-head comparison of fresh-frozen and irradiated graft in a randomized fashion. In that regard, level I evidence supporting the use of fresh-frozen tissue over irradiated bone is lacking.

Conclusions:

The use of allograft bone in orthopaedic surgery has provided solutions to difficult problems. The choice of the appropriate amount of tissue processing to optimize patient outcomes is not without controversy. To our knowledge, there is no report demonstrating that irradiated tissue reduces clinical infection in recipients of allograft bone. However, there are reports showing that terminal sterilization with γ irradiation improves end-product sterility, and thereby reduces

allograft wastage through pre-implant rejection. The safety of salvaging contaminated materials with terminal sterilization has come into question. Clinical data comparing outcomes of fresh-frozen vs. irradiated grafts are limited. However, with careful interpretation, there is a trend towards favorable biological and mechanical results reported with fresh frozen allograft, in particular with impaction studies in revision hip arthroplasty. Although avoiding infection is of great importance in reconstructive orthopaedic surgery, it is difficult to envision how utilizing product with inferior biological and biomechanical qualities would not risk reducing long-term survivorship of reconstructive orthopaedic surgery. To universally advocate γ irradiation of all products in the absence of evidence demonstrating a reduction in infection rates seems irrational. For these reasons, we feel that appropriate candidate screening and improved quality control with tissue retrieval and handling may be a more appropriate way of focusing resources to improve allograft quality as compared to terminal processing with γ irradiation.

Future directions:

A well-controlled, randomized clinical trial using identical techniques and implants, comparing fresh-frozen and irradiated tissue would be a significant contribution to the medical literature. Given the relative rarity of candidates for this type of surgery, as well as the myriad of techniques and implants available, it is difficult to envision how this might be accomplished in the absence of a multi-centered approach. Further, this type of study requires years of rigorous follow-up before trends emerge. Alternate methods of sterilization with less deleterious effect on the biological and material properties of allograft bone is also of research interest. Some early reports of cleansing solutions have emerged, but to date are not universally available, and clinical studies are lacking.

Tables

Table 1. Summary of experimental literature.

	Fresh-Frozen Allograft	***Irradiated Allograft***
Immunogenicity	Reduced vs. fresh	Reduced vs. fresh frozen
Sterility	Donor and handling dependent	Improved sterility (most bacteria, some viruses)
Strength	Stronger in bending, fatigue strength Larger energy fracture	Weaker in bending, fatigue strength Lower energy fracture
Biology	No effect on BMP-7 or osteoblast differentiation	Reduced BMP-7 expression, reduced osteoblast differentiation

Table 2. Summary of clinical studies of impaction allografting.

Fresh-frozen Allograft	***Irradiated Allograft***
Improved radiographic incorporation	Lower incidence of radiographic incorporation
Less stem subsidence	More stem subsidence
Favorable long-term studies	Shorter follow-up times reported

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